THE AMERICAN SOCIETY OF Breast Surgeons

Resource Guide

Endocrine Therapy for the Management and Risk Reduction of Hormone Receptor Positive Breast Cancer

Endocrine therapy is an effective treatment for breast cancer. It is used in the adjuvant setting for hormone receptor positive (HR+) invasive breast cancer and ductal carcinoma in situ, as neoadjuvant therapy for HR+ invasive cancer, and for reducing the risk of HR+ breast cancer in high-risk women*.

In today's treatment paradigm it is important for breast surgeons to understand the indications for endocrine therapy and be comfortable prescribing and managing adverse events of endocrine therapy. This will allow more patients to be offered neoadjuvant and risk-reducing endocrine therapy in their community and for surgeons to be involved more actively in the management and outcomes of their patients with breast cancer or high risk. This guide is meant to be a resource for breast surgeons and does not replace treatment guidelines from the National Comprehensive Cancer Network or the American Society of Clinical Oncology.

*For the purposes of this guideline, the terms "woman" and "women" refer to individuals assigned female at birth (AFAB). The terms "man" and "men" refer to individuals assigned male at birth. Patient management recommendations in this guideline apply to those AFAB unless noted otherwise.

Key Points

Classes of Drugs

- Available endocrine therapies include:
  - Selective estrogen receptor modulators (SERMs)—tamoxifen and raloxifene (Note—raloxifene is used for risk reduction but not for cancer therapy)
  - Aromatase inhibitors (AIs)—anastrozole, letrozole, and exemestane
  - Selective estrogen receptor down regulators (SERDs)—fulvestrant and elacestrant (Note—SERDs are used for cancer therapy but not for risk reduction)
- Tamoxifen and raloxifene both increase the risk of venous thromboembolic events; tamoxifen increases the risk of endometrial cancer, and this increased risk is most pronounced in older patients.
- Premenopausal women for whom therapeutic endocrine therapy is recommended can use AIs with ovarian function suppression (OFS).
- AIs contribute to bone loss and osteoporotic fracture. Bone mineral density should be assessed prior to a patient starting an AI and reassessed every 1-2 years.

Risk Reduction

- Endocrine therapy should be offered for risk reduction to women with atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ and to those with a 5-year risk $\geq$3% using the Gail model or with a 10-year risk $\geq$5% using Tyrer-Cuzick.
- Endocrine therapy reduces the risk of developing estrogen receptor positive (ER+) breast cancer by 50% or more in the above groups of patients; options include tamoxifen (the only option for premenopausal women), raloxifene, exemestane, and anastrozole.

Neoadjuvant Endocrine Therapy

- Neoadjuvant endocrine therapy is an option for postmenopausal patients with ER+ tumors. Neoadjuvant endocrine therapy in ER+ breast cancer can enable breast conservation and allows evaluation of tumor endocrine responsiveness to guide additional therapy.

Adjuvant Endocrine Therapy

- Many premenopausal patients with ER+ breast cancer benefit from OFS even with tamoxifen.
- Postmenopausal patients with invasive breast cancer (regardless of hormone receptor status) should be offered a bisphosphonate to reduce the risk of disease recurrence.
- Extended endocrine therapy reduces recurrence and second breast cancer events, but no robust data shows an impact on survival. Patients most likely to benefit from extended endocrine therapy are those with higher risk, node positive disease.
- In addition to clinical factors, genomic assays (such as Breast Cancer Index) provide additional information regarding the risk of distant recurrence and the likelihood of benefit with extended endocrine therapy.
- Side effects are common with endocrine therapy, but multiple options exist to reduce and manage those side effects.

Outline

🔗–Section 1

Classes of Drugs

1A. Selective Estrogen Receptor Modulators (SERMs)

- Tamoxifen
- Raloxifene

1B. Aromatase Inhibitors (AIs)

- Anastrozole
- Letrozole
- Exemestane

1C. Selective Estrogen Down Regulators (SERDS)

- Fulvestrant
- Elacestrant

🔗–Section 2

Risk-Reducing Endocrine Therapy

2A. Eligible Patients

2B. Efficacy of Risk-Reducing Endocrine Therapy

- Tamoxifen trials
- Raloxifene trials
- Aromatase inhibitor trials

🔗–Section 3

Therapeutic Endocrine Therapy

3A. Ductal Carcinoma in Situ

3B. Endocrine Therapy for the Management of Hormone Receptor-Positive Invasive Breast Cancer

3C. Neoadjuvant Endocrine Therapy

3D. Length of Endocrine Therapy

3E. Endocrine Therapy in Special Populations

- Patients Desiring Pregnancy
- Elderly or Frail Patients
- Male Breast Cancer Patients

3F. Indication for the Addition of Non-Endocrine Therapies

- Bone-Directed Therapy
- Cyclin-Dependent Kinase Inhibitors

🔗–Section 4

Genomic Tumor Evaluation of Hormone Receptor-Positive, HER2-Negative Breast Cancer to Guide Use of Chemotherapy

4A. Oncotype DX

4B. MammaPrint

4C. EndoPredict

4D. Prosigna

🔗–Section 5

Genomic Tumor Evaluation of Hormone Receptor-Positive, HER2-Negative Breast Cancer to Guide Use of Extended Endocrine Therapy

5A. Breast Cancer Index

🔗–Section 6

Management of Endocrine Therapy Side Effects

- **6A. Vasomotor Symptoms**
- **6B. Thromboembolic Events**
- **6C. Endometrial Effects**
- **6D. Vaginal Atrophy/Dyspareunia**
- **6E. Osteopenia/Osteoporosis**
- **6F. Musculoskeletal Complaints**
- **6G. Weight Gain**

🔗–Tables

List of Abbreviations

AI	Aromatase inhibitor
ASCO	American Society of Clinical Oncology
BCFI	Breast cancer-free interval
BCS	Breast conserving surgery
BCSS	Breast cancer-specific survival
CI	Confidence interval
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DVT	Deep venous thrombosis
ER	Estrogen receptor
HR	Hazard ratio
HR+	Hormone receptor positive
IBC	Invasive breast cancer
LCIS	Lobular carcinoma in situ
NCCN	National Comprehensive Cancer Network
NET	Neoadjuvant endocrine therapy
OFS	Ovarian function suppression
OS	Overall survival
PE	Pulmonary embolism
PFS	Progression-free survival
PgR	Progesterone receptor
RFS	Recurrence-free survival
RR	Relative risk (rate ratio)
RR-ET	Risk-reducing endocrine therapy
SERD	Selective estrogen receptor degrader
SERM	Selective estrogen receptor modulator
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
ZA	Zoledronic acid

Section 1 – Classes of Drugs

Section 1A – Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) act as estrogen agonists or antagonists depending on the target tissue. There are multiple drugs in this category, including tamoxifen, which has been used for decades to prevent and treat hormone receptor positive (HR+) breast cancer in pre- and postmenopausal women and in men. The SERM raloxifene reduces the risk of HR+ breast cancer in high-risk postmenopausal women but is not used to treat patients already diagnosed with HR+ breast cancer.

Tamoxifen[1] and raloxifene[2] competitively inhibit the action of estradiol by binding to the estrogen receptor (ER). Both exert an antiestrogenic effect on breast tissue and an estrogenic effect on the skeletal system; tamoxifen, but not raloxifene, is an estrogen agonist in the uterus. Both lower cholesterol and increase the risk of venous thromboembolism (VTE). A family history of VTE is not a contraindication to SERM use, but SERMs should be used cautiously in those with a personal or family history suggestive of a coagulopathy. Frequent side effects include vasomotor symptoms (VMS), increased vaginal discharge, arthralgias and myalgias, and peripheral edema.

Tamoxifen

Tamoxifen indications include:

- Treatment of HR+ invasive breast cancer (IBC) in pre- and postmenopausal women (20 mg daily for at least 5 years),
- Treatment of HR+ ductal carcinoma in situ (DCIS) in pre- and postmenopausal women (20 mg daily for 5 years; 5 mg daily for 3-5 years is an option for women unable to tolerate or unwilling to take the standard 20 mg dose),
- Treatment of IBC in men (20 mg daily for at least 5 years), and
- Risk reduction in high-risk women aged 35 years and older (20 mg daily for 5 years; 5 mg daily for 3-5 years is an option for women unable to tolerate or unwilling to take the standard 20 mg dose).

Tamoxifen contraindications include:

- The need for anticoagulation therapy or a history of pulmonary embolism (PE) or deep venous thrombosis (DVT), and
- Pregnancy or breastfeeding.

Tamoxifen warnings:

- Tamoxifen increases the risk of endometrial hyperplasia, polyps, and malignancy (primarily adenocarcinoma);
- Tamoxifen has been associated with cataracts and increased liver enzymes; and

- Tamoxifen efficacy may be affected by coadministration of drugs requiring metabolism through the P450 CYP2D6 enzyme system.

Raloxifene

Raloxifene indications include:

- Treatment and prevention of postmenopausal osteoporosis (60 mg daily), and
- Risk reduction in high-risk postmenopausal women aged 35 years and older (60 mg daily for 5 years).

Raloxifene contraindications include:

- A history of PE, DVT, or retinal vein thrombosis,
- Premenopausal status, and
- Pregnancy or breastfeeding.

Raloxifene warnings:

- Raloxifene may increase serum triglycerides in patients with a history of exogenous hormone-dependent hypertriglyceridemia; and
- Potential drug interactions include cholestyramine, warfarin, and other heavily protein-bound drugs.

Section 1B – Aromatase Inhibitors

In postmenopausal women, most estrogen production occurs in adipose tissue, the adrenal glands, muscle, and breast tissue, where aromatase converts androgens into estrogen. The nonsteroidal aromatase inhibitors (AIs) anastrozole[3] and letrozole[4] bind reversibly to aromatase, while exemestane[5], a steroidal AI, irreversibly binds to aromatase.

The resulting decrease in estrogen negatively impacts bone health and serum cholesterol and increases the risk of cardiac events. Common side effects include arthralgias, hair thinning, and vaginal atrophy and dryness. Standard doses for therapeutic and risk-reducing indications are anastrozole 1 mg daily, letrozole 2.5 mg daily, and exemestane 25 mg daily.

Anastrozole, letrozole, and exemestane

AI Indications include:

- The treatment of HR+ breast cancer;
- Clinical trial data supports the off-label use of anastrozole and exemestane as risk-reducing agents for high-risk women.

AI contraindications and warnings:

- All 3 AIs are approved for use in postmenopausal women;
- All 3 AIs are associated with a reduction in bone density, which should be assessed prior to AI initiation and every 1-2 years during AI therapy;
- Letrozole and anastrozole may increase serum cholesterol; and
- Patients with pre-existing ischemic heart disease experienced more ischemic cardiac events with anastrozole.

Section 1C – Selective Estrogen Receptor Down Regulators

Until 2023, the only selective estrogen receptor down regulator (SERD) available was fulvestrant[6], which binds to and degrades the ER. The maintenance dose is 500 mg monthly by intramuscular injection. Fulvestrant is indicated for patients with metastatic breast cancer who progress on AIs or who have compliance issues with daily oral medication[7]. Common side effects include injection site reactions, arthralgias, nausea, and elevated liver enzymes. Fulvestrant is currently being evaluated as neoadjuvant endocrine therapy for operable breast cancer in the ALTERNATE trial[8].

In 2023, the Food and Drug Administration (FDA) approved elacestrant, the first oral SERD, for the treatment of metastatic HR+ breast cancer with an ESR1 mutation that has progressed on at least one line of prior therapy[9]. In the EMERALD trial, elacestrant significantly improved progression free survival (PFS) compared with fulvestrant in patients with ESR1-mutated tumors[10]. An ongoing clinical trial is evaluating the oral SERD giredestrant for early stage, ER+, HER2 negative breast cancer[11].

Fulvestrant

Fulvestrant indications include:

- HR+, HER2 negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy;
- HR+ advanced breast cancer in postmenopausal women with disease progression on endocrine therapy;
- HR+, HER2 negative advanced or metastatic breast cancer in postmenopausal women, in combination with ribociclib, either as initial endocrine therapy or with disease progression on endocrine therapy; and
- HR+, HER2 negative advanced or metastatic breast cancer, in combination with palbociclib or abemaciclib, with disease progression on endocrine therapy.

Fulvestrant contraindications and warnings:

- Fulvestrant should not be used in women who are pregnant or breastfeeding; and
- Fulvestrant should be used with caution in patients with increased bleeding risk.

Elacestrant

Elacestrant indications include:

- Treatment of postmenopausal women or adult men with ER+, HER2 negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

Elacestrant contraindications and warnings:

- Elacestrant may cause elevations in serum cholesterol and triglycerides; and
- Elacestrant should not be used in women who are pregnant or breastfeeding.

Section 2 – Risk-Reducing Endocrine Therapy

Section 2A – Eligible patients

Risk-reducing endocrine therapy (RR-ET) roughly halves the risk of HR+ breast cancer in high-risk women, and the protection is durable. Patients most likely to benefit are those with significantly elevated risk, especially those with atypia (atypical ductal hyperplasia [ADH] or atypical lobular hyperplasia [ALH]) or lobular carcinoma in situ (LCIS). In fact, risk reduction is as high as 75%[12] for patients with ADH or ALH, which are strongly estrogen-driven. RR-ET also reduces the likelihood of benign disease and biopsies[13] and may decrease breast density[14]. It does not, however, impact survival. Of note, few women with hereditary cancer predisposition were included in the RR-ET trials.

Almost all RR-ET data is from women aged 35 years and older; data is additionally limited to cis-gender women. Tamoxifen is the only option for premenopausal women; women taking tamoxifen should not be pregnant or breastfeeding or imminently planning pregnancy and need effective contraception. Postmenopausal women are eligible not only for tamoxifen but for raloxifene, anastrozole, or exemestane; the choice is guided by patient comorbidities and preference and by drug side effects, adverse events, and cost. Women aged 70 years and older may benefit from RR-ET depending on their short-term risk (e.g. those with atypia or LCIS), overall health, and life expectancy.

Consensus guidelines[15,16] recommend offering RR-ET to women with:

- ADH, ALH, or LCIS;
- An estimated 5-year breast cancer risk $\geq$3% using the National Cancer Institute Breast Cancer Risk Assessment Tool (modified Gail score; RR-ET can be offered at a 5-year risk as low as 1.7%);
- An estimated 10-year breast cancer risk $\geq$5% using the International Breast Intervention Study (IBIS)/Tyrer-Cuzick (TC) Risk Calculation;
- A relative risk 4 times the population average for those aged 40-44 years;
- A relative risk 2 times the population average for those aged 45-69 years;
- A history of thoracic radiation therapy prior to age 30; or
- A highly- or moderately-penetrant breast cancer predisposition gene.

Unfortunately, uptake of RR-ET is low[17], largely because of actual and feared side effects. Reassuringly, most side effects and adverse event risks return to baseline after medication cessation. Charts published by Freedman et al weigh the risks and benefits of tamoxifen and raloxifene for women with and without a uterus, based on the degree of risk elevation; these may help with RR-ET decision-making[18].

Section 2B – Efficacy of Risk-Reducing Endocrine Therapy

Placebo-controlled tamoxifen trials

Four large trials compared the impact of tamoxifen 20 mg daily with that of placebo on breast cancer risk: Royal Marsden, IBIS-I, NSABP P-1, and the Italian Tamoxifen Prevention study. Participants in the Royal Marsden trial received tamoxifen 20 mg or placebo for 8 years, while the other 3 trials used a 5-year course of tamoxifen 20 mg or placebo. More recently, the Italian TAM-01 trial compared a 3-year course of tamoxifen 5 mg with placebo; these trials are summarized in Table 1.

- The Royal Marsden[19] trial included women aged 30-70 years and at increased risk based on family history. There was a nonsignificant reduction in IBC overall or for ER+ disease during the treatment period, but tamoxifen reduced ER+ disease risk by 52% in the post-treatment period. Tamoxifen increased the risk of endometrial cancer, approaching statistical significance. There was no significant difference in VTE, stroke, or fracture risk.
- IBIS-I[20] enrolled high risk women (defined by family history or benign disease), aged 35-70 years. At 16 years, ER+ IBC risk was reduced by a third, and this effect was durable. DCIS risk was also reduced, but only during the first 10 years. The risk reduction benefit was greatest for women aged ≤50 years. Endometrial cancer risk and VTE risk were significantly higher, but only during years 0-5 and years 1-10, respectively. There was no significant difference in cardiovascular events, stroke, mortality, or breast cancer-specific mortality.
- The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (NSABP P-1)[12] included patients who were: (1) aged ≥60 years (without qualifying risk calculation) or (2) aged 35-59 years with a 5-year risk >1.66% or with LCIS. Risk reduction was 43% for IBC, 37% for DCIS, and 69% for ER+ disease. Risk reduction was 46% for patients with LCIS and 75% for those with atypia (56% and 86% risk reduction, respectively, were reported in the initial publication with shorter follow-up[21]). Endometrial cancer and stroke were significantly more common with tamoxifen, driven primarily by events in women
  >50 years of age; the risk of PE was elevated regardless of age. Tamoxifen reduced fracture risk by 32%. Older patients and those on tamoxifen longer were more likely to develop cataracts.
- Italian Tamoxifen Prevention Study[22] participants were all status post hysterectomy, but not all were high risk. Tamoxifen reduced breast cancer by 76% only for high-risk women (defined by height, menarche, menopause status, and parity). Adverse events included increased triglycerides, VTE, and cardiac arrhythmia or atrial fibrillation.

A meta-analysis[23] confirmed that tamoxifen had no effect on ER negative breast cancers but reduced ER+ cancers by 48%. Rates of endometrial cancer were increased in all tamoxifen prevention trials (consensus relative risk [RR] 2.4; 95% confidence interval [CI]

1.5-4.0), as were VTEs (RR 1.9; 95% CI 1.4-2.6). There was no effect on non-breast cancer mortality.

Side effects, adverse events, and fear of these events limit patient adherence to RR-ET. The TAM-01[24] trial compared 5 mg of tamoxifen for 3 years with placebo for patients with ADH, LCIS, or ER+/ER unknown DCIS. At a mean follow-up of 9.7 years, this low dose reduced the likelihood of IBC or DCIS by 42% compared with placebo. There was 1 endometrial cancer in the tamoxifen arm and 1 VTE in each group. Overall hot flash score was not significantly higher with tamoxifen. Because of the robust data on the higher dose of tamoxifen, though, 20 mg for 5 years remains the standard. However, for women unwilling to take or unable to tolerate the standard dose, 5 mg daily for 3-5 years is an option[15,16].

Key risk-reduction raloxifene trials

Several trials compared raloxifene with placebo; one trial compared raloxifene with tamoxifen. The dose of raloxifene in all trials was 60 mg daily, except for the MORE trial which randomized participants to raloxifene at either 60 mg or 120 mg daily or to placebo (Table 1).

- The MORE (Multiple Outcomes of Raloxifene Evaluation) trial[25] randomized average risk, postmenopausal women with osteoporosis to raloxifene at one of 2 doses or placebo for 4 years. Raloxifene reduced the risk of ER+ IBC by 90%. Vertebral fracture risk and bone density were significantly better with raloxifene, although there was no significant difference in non-vertebral fractures.
- For the CORE (Continuing Outcomes Relevant to Evista) trial[26], MORE trial participants could extend their original therapy assignment by 4 years; participants randomized originally to either dose of raloxifene received 60 mg for the CORE extension. IBC risk was reduced 76% during the 8-year study period. There was no significant difference in endometrial cancer risk with raloxifene, but VTE risk was doubled.
- The RUTH (Raloxifene Use for The Heart) trial[27] enrolled patients with heart disease or with cardiac risk factors. IBC risk was reduced 44% with raloxifene, but there was no impact on cardiac outcomes. Raloxifene increased VTE events and reduced vertebral fractures.
- The STAR (Study of Tamoxifen and Raloxifene) trial[28] randomized women with a 5-year Gail calculation of >1.67% or with LCIS to tamoxifen or raloxifene. At 10 years, raloxifene was moderately inferior to tamoxifen for reducing IBC but caused fewer endometrial cancers and VTEs. Impact on noninvasive breast cancer was not significantly different between the 2 drugs, especially with longer follow-up.

A meta-analysis[23] of tamoxifen or raloxifene versus placebo trials confirmed no impact on ER negative disease or non-breast cancer mortality with raloxifene, and like

tamoxifen, raloxifene increased VTE risk. However, raloxifene did not increase the risk of endometrial cancer.

Key risk reduction aromatase inhibitor trials

Using an AI (specifically exemestane or anastrozole) to reduce breast cancer risk is an off-label use, but is supported by 2 randomized, controlled trials (Table 1).

IBIS-II[29] included postmenopausal women (1) aged 60–70 years with a breast cancer RR 1.5 times their age average, (2) aged 45–60 with a 2-fold RR, (3) aged 40–44 with a 4-fold RR, (4) with DCIS, LCIS, atypia, or (5) with a Tyrer Cuzick 10 year risk >5%. IBC and DCIS events were reduced by half, and there was no significant increase in fractures or cardiovascular events with anastrozole.

The MAP.3 (Mammary Prevention 3) trial[30] randomized postmenopausal patients aged ≥35 years to exemestane, exemestane plus celecoxib, or placebo. Inclusion criteria included (1) age ≥60 years, (2) Gail 5 year risk >1.66%, or (3) atypia/LCIS; prior DCIS treated with mastectomy was allowed (2.5% of the total cohort). With a median 3 year follow-up, exemestane reduced IBC by 65%, without significantly increasing fractures or cardiovascular events.

Although not prevention trials, the ATAC (Arimidex, Tamoxifen, Alone or in Combination)[31] and the MAP.17R[32] trials showed fewer contralateral breast cancers with anastrozole versus tamoxifen, and with letrozole versus placebo, respectively, providing additional evidence supporting the risk-reducing benefit of AIs.

Section 3 – Endocrine Therapy for the Treatment of HR+ Breast Cancer

Endocrine therapy is effective adjuvant and neoadjuvant therapy for patients with HR+ breast cancer. Drug selection for an individual patient is influenced by menopause status, comorbidities, contraindications, and the side effect profile.

Tamoxifen is an option for any patient with ER+ and/or progesterone receptor positive (PgR+) invasive or noninvasive breast cancer. In contrast, AI use is limited to postmenopausal patients and premenopausal patients receiving ovarian function suppression (OFS). Overall, clinical trial data shows better outcomes with AIs versus SERMS, but both categories of endocrine therapy improve local, regional, and distant disease-free survival.

Prior to starting adjuvant endocrine therapy for HR+ breast cancer, potential benefit from systemic chemotherapy needs to be assessed (see Section 4). If systemic chemotherapy is needed, endocrine therapy should start after chemotherapy. Endocrine therapy is usually initiated after completion of radiation therapy, but administration with concurrent radiation is an option[33].

Section 3A – Ductal Carcinoma in Situ

Ductal Carcinoma in Situ (DCIS)

Following local therapy for HR+ DCIS, endocrine therapy reduces the risk of recurrence; endocrine therapy for DCIS does not, however, improve survival. NSABP B-24[34] demonstrated that tamoxifen 20 mg daily for 5 years following lumpectomy and radiation therapy led to a significant reduction in recurrence (in-situ or invasive) compared with placebo. As discussed in Section 2, the TAM-01 trial[24], in which 69% of participants had DCIS, showed a 42% reduction in breast cancer events and a 64% reduction in contralateral breast cancers with tamoxifen 5 mg.

Anastrozole, however, was superior to tamoxifen 20 mg in the NSABP B-35 trial[35]: It produced a better breast cancer free interval (BCFI) and disease-free survival (DFS) in women diagnosed with DCIS, but this superiority was limited to women aged <60 years. Tamoxifen was associated with a higher risk of VTE. Despite the benefits of anastrozole, however, overall survival (OS) did not differ between the two arms. IBIS-II-DCIS[36], which also randomized patients with DCIS to tamoxifen or anastrozole, showed noninferiority, but not superiority, of anastrozole.

In women who undergo bilateral mastectomies for DCIS, adjuvant endocrine therapy is not usually recommended[33].

Section 3B – Hormone Receptor Positive Invasive Breast Cancer

Endocrine therapy is indicated for anyone with HR+ invasive disease. It's reasonable, however, to consider omission of endocrine therapy for patients with T1a N0 tumors or for women with favorable pure tubular, mucinous, and cribriform histologies and encapsulated or solid papillary carcinoma[33].

Broadly, endocrine therapy options include tamoxifen or an AI—as with DCIS, raloxifene is not used in the therapeutic setting.

Premenopausal HR+ IBC

Tamoxifen is the only option for premenopausal women in the absence of OFS. Most premenopausal patients who take adjuvant tamoxifen for 5 years are likely to benefit from extended therapy with additional tamoxifen or a transition to an AI, depending on menopause status (length of therapy is discussed in Section 3D). Genomic testing (see Section 5) can be used to help guide this decision.

Premenopausal women may have cessation of menses with chemotherapy; these patients should be treated with tamoxifen until it is clear that they will not resume ovarian function. Menopause may be assessed with laboratory studies (i.e. luteinizing hormone, follicle-stimulating hormone [FSH], and estradiol), but tamoxifen may affect FSH, and these hormones fluctuate throughout perimenopause. A single set of labs is therefore inadequate for confirming menopausal status[33].

Some premenopausal patients benefit from OFS, whether they transition to an AI or remain on tamoxifen. SOFT (Suppression of Ovarian Function Trial)[37] randomized premenopausal women to tamoxifen, tamoxifen plus OFS, or exemestane plus OFS. At a median follow-up of 12 years, DFS was significantly better with tamoxifen plus OFS versus tamoxifen (hazard ratio [HR] 0.82; 95% CI 0.69-0.98). Overall survival was 86.8% with tamoxifen, 89.0% with tamoxifen plus OFS (HR versus tamoxifen alone 0.78; 95% CI 0.60-1.01), and 89.4% with exemestane plus OFS. The impact of OFS was most pronounced with higher risk disease.

In TEXT (Tamoxifen and Exemestane Trial)[38], patients were randomized to tamoxifen plus OFS or exemestane plus OFS. Exemestane plus OFS produced superior 12-year DFS versus tamoxifen plus OFS (12-year DFS HR 0.79; 95% CI 0.70-0.90), but not OS (HR 0.93; 95% CI 0.78-1.11). The DFS benefit was most pronounced in women at higher risk for recurrence (age <35 years, tumors >2 cm, or high grade tumors).

Side effects, including hypertension and impaired glucose control, were more frequent with the use of OFS. Importantly, osteoporosis impacted 3.9% of tamoxifen patients in SOFT versus 7.2% of those receiving tamoxifen plus OFS and 14.8% of those receiving exemestane plus OFS. Vaginal dryness and dyspareunia were most frequent with exemestane plus OFS[37,38].

Postmenopausal HR+ IBC

Postmenopausal patients with HR+ breast cancer are usually managed with an AI, taken for at least 5 years. Tamoxifen is an option for postmenopausal patients unable to tolerate or unwilling to take an AI. Additional information comparing tamoxifen with AIs is discussed in Section 3D, which also discusses the length of endocrine therapy.

Postmenopausal patients with IBC should also be offered bone directed therapy with bisphosphonates (see Section 3F).

Section 3C – Neoadjuvant Endocrine Therapy

For patients with HR+, HER2 negative disease, neoadjuvant chemotherapy offers several benefits, including assessment of treatment response, improving rates of successful breast conservation, and limiting the extent of axillary surgery. For patients with no clear indications for neoadjuvant chemotherapy, neoadjuvant endocrine therapy (NET) may provide similar benefits. In addition, NET may bridge the time from diagnosis to surgery (e.g. to allow for reconstruction planning, smoking cessation or genetic testing, or as was needed during the pandemic). While NET trials often treated patients for 3-6 months preoperatively, there is no consensus on the ideal length of NET[33,39].

For postmenopausal patients with strongly ER+ tumors, neoadjuvant AI therapy is superior to neoadjuvant tamoxifen and is associated with less toxicity than neoadjuvant chemotherapy[40-42]. In a meta-analysis of 20 studies comparing neoadjuvant therapy regimens[43], AIs produced a similar clinical response rate, radiological response rate, and breast conserving surgery (BCS) rate to those seen with neoadjuvant chemotherapy, while producing a higher clinical response rate, radiological response rate, and BCS rate than neoadjuvant tamoxifen. Pathologic complete responses, however, are uncommon. There are limited data on the use of NET in premenopausal women, so one consensus guideline currently recommends against off-trial NET for that population[39].

Several NET clinical trials assessed ki-67 on a repeat core biopsy after a period of endocrine therapy. Patients with a starting ki-67 <10% do well with endocrine therapy alone and repeating the ki-67 after a period of NET does not add prognostic information[44]. For those with a higher starting ki-67, however, a decrease in ki-67 is prognostic[8,44]. For patients treated with NET, the preoperative endocrine prognostic index (PEPI) score calculated at surgery is prognostic. Patients with a PEPI score of 0 (defined as ypT1/2, ypN0, ki-67 <2.7%, and ER Allred score of 3-8) have a low risk of recurrence with endocrine therapy alone[45].

Due to lack of prospective data, consensus guidelines do not currently recommend using ki-67 or PEPI score for directing patient management[33,39]. An ongoing clinical trial[46] is assessing the use of ki-67 and 21-gene Recurrence Score to direct systemic therapy decisions in pre- and postmenopausal women.

Section 3D – Length of endocrine therapy

In 1998, a meta-analysis of 55 trials compared adjuvant tamoxifen with no tamoxifen[47]. For patients with ER+/ER unknown tumors, one year of tamoxifen reduced recurrence by 21%, 2 years by 29%, and 5 years by 47%. Mortality and contralateral breast cancers were similarly reduced. This effect was not seen in patients with ER negative disease. Although both node negative and node positive patients benefitted, the latter benefited most.

NSABP B-14 participants (all node negative) who were randomized to tamoxifen (versus placebo) for the first 5 years of endocrine therapy were re-randomized to tamoxifen or placebo for an additional 5 years. Five years of tamoxifen produced better DFS, recurrence free survival (RFS), and OS compared with extended therapy[48]. The consensus was to recommend 5 years of tamoxifen outside a clinical trial.

Unfortunately, many ER+ cancers recur years after a patient completes a 5-year course of endocrine therapy. Patients at a higher recurrence risk, such as those with positive nodes, larger tumors, or who need chemotherapy, do benefit from extended endocrine therapy. Reducing the risk of second breast cancers explains some of the benefit of continuing endocrine therapy. There is, however, a paucity of data showing an OS benefit with extended endocrine therapy,

An American Society of Clinical Oncology (ASCO) Clinical Practice Guideline[49] included a systematic review on the optimal duration of endocrine therapy; key studies are summarized in Table 2.

Trials evaluating 5 years of tamoxifen following 5 years of tamoxifen

In addition to NSABP B-14, 2 other trials evaluated the benefit of continuing tamoxifen for an additional 5 years—ATLAS[50] and ATTOM[51]. Both showed better DFS, breast cancer specific survival (BCSS), and OS with extended tamoxifen therapy, but more PEs and endometrial cancers.

Trials evaluating an AI following tamoxifen

- In MA.17[52] letrozole started after 5 years of tamoxifen reduced recurrence by 43% versus placebo at an interim analysis. The trial was unblinded and participants randomized to placebo were offered letrozole. Extended letrozole improved DFS and, for node positive patients, improved OS.
- NSABP B-33[53] randomized patients to exemestane or placebo. Based on the unblinding of MA.17, this trial was also unblinded and placebo group patients were offered exemestane. Extended therapy reduced recurrences by 32%. Patients most likely to benefit were younger, had larger tumors, were node positive, received prior chemotherapy (so had higher risk disease), and were both ER+ and PgR+.

- The ABCSG 6A trial[54] compared 3 years of anastrozole with no further therapy following 5 years of tamoxifen, in effect comparing 5 with 8 years of endocrine therapy. The extension improved DFS because of a reduction in distant metastasis.
- The Italian GIM-4 trial[55] compared an additional 2 or 3 with 5 years of letrozole following 2-3 years of tamoxifen. Extended therapy reduced recurrences at 12 years (DFS 67% versus 62%; HR 0.78; 95% CI 0.65-0.93).
- DATA[56] similarly compared 3 versus 6 years of anastrozole following 2-3 years of tamoxifen. There was a numeric but not statistically significant advantage to extended therapy. For patients with tumors that were both ER+ and PgR+, however, DFS was significantly improved.

Trials evaluating extended AI therapy

- In NSABP B-42[57], patients who received 5 years of endocrine therapy (primarily an AI) were randomized to 5 years of letrozole or placebo. Extended therapy improved DFS, especially for patients who received tamoxifen as part of their initial regimen, and reduced recurrences without increasing the risk of fracture.
- MA.17R[58] participants were randomized to 5 years of letrozole or placebo following 5 years of an AI. Most study participants received tamoxifen for 5 years prior to starting their 5-year course of AI therapy, however, so MA.17R essentially compared a total 10 to 15 years of endocrine therapy. Ten years of an AI (a total of 15 years of endocrine therapy) improved DFS and reduced contralateral breast cancers, but did not change OS, and fractures were more common even though over half of those patients were on a bisphosphonate.

In the IDEAL, ABCSG 16 and SOLE trials, all patients received 5 years of endocrine therapy, which usually included an AI, but study dosing schedules during years 5-10 differed.

- The IDEAL trial[59] showed that 7.5 years of endocrine therapy produced equivalent recurrence risk to that with 10 years. Second primary breast cancer events were higher, however.
- Similarly, ABCSG 16[60] compared an additional 2 versus 5 years of anastrozole, essentially comparing 7 with 10 years of endocrine therapy, and did not show superiority with a longer therapy regimen. As in MA.17R, fractures were more common, despite equivalent use of bone-targeted therapy.
- Participants in the SOLE trial[61] were node positive, so presumed to benefit from extended therapy; all received letrozole during years 6-10. During the first four years of the trial (endocrine therapy years 6-9), participants took letrozole for 9 months on, 3 months off. During the last year of the study (endocrine therapy year 10), they took letrozole continuously. Using the intermittent regimen did not significantly impact DFS, OS, or adverse events.

Collectively, these studies show that patients most likely to benefit from extended therapy are those with high risk, node positive disease, but there is not yet robust data

showing a significant improvement in OS. Patients taking tamoxifen for 5 years likely benefit from additional endocrine therapy with either another 5 years of tamoxifen or 2-5 years of an AI. ASCO[49] therefore recommends that anyone with node positive disease be offered 10 years of endocrine therapy. Node negative patients without other high risk features, like grade 3 disease, likely only need 5 years, and there is no role for extending endocrine therapy beyond 10 years.

Genomic assays (primarily Breast Cancer Index [BCI], discussed in Section 5) provide additional guidance regarding the potential benefit of extended endocrine therapy.

Section 3E – Special populations

Desire for pregnancy

For many women, a 5-year course of tamoxifen impacts their ability to conceive and carry a pregnancy to term. In these situations, an interruption in endocrine therapy can be entertained.

The POSITIVE[62] (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial followed premenopausal women who received 18-30 months of endocrine therapy prior to stopping to attempt pregnancy. There was no significant difference in recurrence risk compared with a matched cohort from the SOFT/TEXT trials (HR 0.81; 95% CI 0.57-1.15). Additionally, the low rate of birth defects (2.2%) was similar to that in the general population.

At least 18 months of tamoxifen is recommended prior to trying to conceive, preferably 2 years. Tamoxifen is potentially teratogenic and should be stopped 2-3 months prior to attempted conception.

Primary endocrine therapy in the frail or elderly

After the age of 70 years, the percent of breast cancers that are ER+ rises[63]. Patients older than 80 years present with higher stage breast cancer than those aged 65-75 years, presumably due to cessation of routine screening[64]. In these patients, NET may allow downstaging of the disease, while primary endocrine therapy may itself be a reasonable option in those with comorbid conditions and poor functional status.

Studies comparing up-front surgery with tamoxifen have shown superior DFS or PFS with surgery, but little difference in OS[65-68]. In an observational study[69], for women aged 70 years and older treated with either primary endocrine therapy (tamoxifen or an AI) or with surgery, 5-year OS and BCSS were similar. In fact, most women died from non-breast cancer causes, especially with increasing age. Eventual progression rate was 45.0% and the median time to progression was 49 months. BCSS was better for patients under age 80 undergoing primary surgery (versus primary endocrine therapy) but this was not

true for those 80 years of age and older. Most of the studies evaluating primary endocrine therapy in elderly women used tamoxifen, but an AI is likely superior given higher response rates.

Online tools assess frailty and treatment-related morbidity and may guide therapy. These include the Cancer and Aging Research Group Chemotherapy Toxicity Tool[70], mortality calculators at ePrognosis[71], and the American College of Surgeons Surgical Risk Calculator[72].

Male breast cancer

Male breast cancer accounts for about 1% of all breast cancers[33]. In general, therapy recommendations are extrapolated from the treatment of female breast cancer. Therapy options mirror those for female patients.

Tamoxifen is the preferred endocrine therapy for males with HR+ disease; when tamoxifen is contraindicated, AIs—but only with a gonadotropin-releasing hormone (GnRH) analog—are an option[33,73].

Section 3F – Indications for the Addition of Non-Endocrine Therapies

Bone-directed therapy

Patients who are postmenopausal (natural or chemotherapy-induced), on AI therapy, and/or receiving OFS are at risk for osteopenia, osteoporosis, and fragility fracture. The use of bone-modifying agents to mitigate these adverse events is discussed in Section 5E.

Separate from maintaining bone density, studies have shown that bisphosphonates (zoledronic acid [ZA], ibandronate, or clodronate) reduce the risk of disease recurrence (primarily in the bone) while improving BCSS and OS in postmenopausal women[74]. Per ASCO[75], all postmenopausal patients with IBC (regardless of ER or HER2 status) and eligible for systemic therapy should be offered one of these 3 bisphosphonates.

Predict[76] provides an estimate of the absolute benefit of adding bisphosphonate therapy. The absolute benefit for most women, however, is small, and the National Comprehensive Cancer Network (NCCN) recommends bisphosphonates only for postmenopausal women with node positive or high risk, node negative disease (regardless of receptors)[33]. Two years of zoledronic acid is noninferior to 5 years[77].

Cyclin Dependent Kinase 4/6 Inhibitors (CDK4/6i)

Patients with advanced or high risk disease may benefit from the addition of a CDK4/6i to endocrine therapy. Based on improved invasive DFS in the MONARCH-E trial[78], the FDA approved abemaciclib in combination with endocrine therapy for HR+, HER2

negative, node positive early stage breast cancer at high risk of recurrence. Ribociclib and palbociclib, in combination with an AI or fulvestrant, are approved for advanced and metastatic HR+, HER2 negative breast cancer[79,80].

Section 4 – Genomic Tumor Evaluation of Hormone Receptor-Positive, HER2-Negative Breast Cancer to Guide Use of Chemotherapy

Treatment of HR+ breast cancer with endocrine therapy is the standard of care. Depending on recurrence risk, many patients also receive chemotherapy. Traditional risk factors for recurrence include large tumor size, node disease, and higher grade. Management of systemic therapy has since evolved, and tumor biology is a key determinant of this decision.

Genomic tumor assays reflect biology and provide additional information regarding prognosis and the potential benefit of chemotherapy. Appropriate use of genomic testing by the breast surgeon can reduce unnecessary treatment delays and identify patients who may or may not benefit from neoadjuvant chemotherapy. When using genomic testing to choose between neoadjuvant chemotherapy and endocrine therapy, testing needs to be performed on the core biopsy specimen; these results are largely consistent with those from a surgical specimen[81].

The use of genomic assays to guide systemic therapy recommendations is limited to patients with HR+, HER2 negative, N0 or N1 disease. Current NCCN guidelines[33] recommend consideration of genomic testing (specifying the 21-gene Recurrence Score) for postmenopausal patients with tumors >5 mm in size with up to 3 positive nodes and who are candidates for chemotherapy, and for premenopausal patients with node negative tumors measuring 6 mm or larger. Patients with T1b lesions (6-10 mm) with low risk features (grade 1 disease, no lymphovascular invasion), however, can be managed with endocrine therapy alone, as these patients were not included in the TAILORx trial.

Consensus guidelines discuss 4 commercial genomic assays: Oncotype DX 21-gene Recurrence Score, MammaPrint, Prosigna, and EndoPredict for chemotherapy decision making[33,82].

4A. Oncotype DX

The Oncotype DX 21-gene Recurrence Score (RS), which ranges from 0-100[83], is prognostic for the risk of distant recurrence, but additionally can predict the benefit of chemotherapy. Postmenopausal patients with a RS $\geq$26 should receive chemotherapy in addition to endocrine therapy; postmenopausal women with T1b or larger and N0 or N1 disease and for whom genomic testing was not performed may receive chemotherapy in addition to endocrine therapy or endocrine therapy alone.

Premenopausal patients with a RS $\leq$15 should receive endocrine therapy with or without OFS. Guidelines recommend either chemotherapy plus endocrine therapy or endocrine therapy with or without OFS for premenopausal patients in whom the 21-gene RS was not performed or for those with a RS of 16-25. Chemotherapy is recommended for patients with a RS of 26 or higher.

TAILORx (Trial Assigning IndividuaLized Options for Treatment)[84] enrolled patients with HR+, HER2 negative, node negative breast cancer. Those with a RS ≤10 received adjuvant endocrine therapy and those with a RS ≥26 received both chemotherapy and endocrine therapy. Roughly 70% of the total cohort had a RS 11-25, and these participants were randomized to endocrine therapy alone or both chemo- and endocrine therapy. Endocrine therapy alone was noninferior to the combination of chemo- and endocrine therapy for invasive disease-free recurrence, second primary breast cancer, freedom from distant recurrence, and OS in women over 50. For participants ≤50 years of age and with a RS 16-25, however, the addition of chemotherapy did lower the risk of distant recurrence.

A 12-year follow-up[85] presented in 2022 confirmed these results: invasive DFS was 75.9% for those with a RS ≤10, 76.8% for those with a mid-range RS randomized to endocrine therapy alone, 77.4% for those with a mid-range RS randomized to chemo-endocrine therapy, and 65.9% for those with a RS ≥26 and treated with both chemo- and endocrine therapy. OS ranged from 87.0% in the high risk group to 89.8% in the other 3 groups. The update also showed that, for women with low RSs and treated with endocrine therapy alone, recurrence was more common after 5 years than in the initial 5 years; women with high RSs had a high risk of recurrence despite the addition of chemotherapy; Black women were more likely to experience recurrence during the first 5 years (but not after that).

Black race was also associated with worse OS in the RS 11-25 cohort (HR 1.51; 95% CI 1.06-2.15) and the entire population (HR 1.41; 95% CI 1.05-1.90). There was no evidence of chemotherapy benefit for any racial or ethnic group in those with a RS of 11-25. Black women were also significantly younger, more likely premenopausal, and had higher grade disease, larger tumors, and higher clinical risk scores[86]. A retrospective review of SEER data[87] also showed that Black women were more likely than White women to have high RSs; node negative Black women had higher breast cancer-specific mortality than node negative White women across RSs.

The RxPonder Trial reported that in postmenopausal women with N1 disease and a RS ≤25, there was no benefit from the addition of chemotherapy to endocrine therapy, with 5-year invasive DFS of 91.9% in the endocrine-only group and 91.3% in the chemo-endocrine group. For premenopausal women in RxPonder, however, invasive DFS at 5 years was 89.0% with endocrine-only therapy but 93.9% with chemo-endocrine therapy[88].

A retrospective analysis of the randomized, prospective SWOG 8814 trial showed no DFS advantage with the addition of chemotherapy to tamoxifen for patients with T1-3 N1-2 (excluding clinical N2 disease), HR+ breast cancer and a RS <18. The RS did, however, predict a DFS benefit with chemotherapy for those with a RS ≥31[89].

4B. MammaPrint

MammaPrint® is a 70-gene assay that predicts the risk of distant recurrence in both node negative and node positive patients[90]. The MINDACT (Microarray in Node-Negative and

1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) trial enrolled patients with T1-3 N0-1 breast cancer. Clinical risk for distant recurrence was assessed using a modified Adjuvant! Online® algorithm (which incorporated ER and HER2 status, tumor size and grade, and node status).

MINDACT[91] showed that the use of chemotherapy did not significantly reduce distant recurrence in patients with HR+, HER2 negative breast cancer with high clinical risk but low genomic risk. Five-year distant metastasis-free survival (DMFS) was 95.9% (95% CI 94.0-97.2) for participants in this cohort randomized to chemotherapy versus 94.4% (95% CI 92.3-95.9) for those randomized to no chemotherapy. Participants who were low risk by both clinical features and Mammaprint had a 5-year distant metastasis free survival (DMFS) of 97.6% (95% CI 96.9-98.2) with endocrine therapy alone. For those at high risk by both clinical and genomic assessment, all of whom received chemotherapy, 5-year DMFS was 90.9% (95% CI 88.0-93.2). Distant recurrence for participants with clinical high risk but low genomic risk (including those with 1-3 positive nodes) did not improve with the use of chemotherapy. Updated analysis[92] showed that for women ≤50 years of age with HR+, HER2 negative disease, with high clinical risk and regardless of genomic risk, chemotherapy improved DMFS by 5%, with the caveat that this was an underpowered exploratory analysis.

For the population of women with low clinical risk, who did not benefit from chemotherapy regardless of genomic MammaPrint risk, ASCO recommends against its use. Similarly, ASCO recommends against it for patients ≤50 years of age with high clinical risk, N0 or N1 disease because they do benefit from chemotherapy. It may, however, inform adjuvant therapy decisions for patients >50 years of age with high clinical risk (N0 or N1)[82].

Up to 15% of early stage breast cancers in the MINDACT trial fell into an UltraLow Risk category[93]. The UltraLow category was defined using several clinical trial cohorts. Approximately 70% of these patients were ER+, but most did not receive systemic endocrine or chemotherapy. Regardless, these patients had 100% BCSS by year 20[94]. The Stockholm tamoxifen (STO-3) trial[95] randomized participants with tumors ≤3 cm, N0, to 2 years of tamoxifen or no additional therapy; those who were disease-free after 2 years of tamoxifen were randomized to no additional therapy or 3 additional years of tamoxifen. Participants with an UltraLow MammaPrint result had 97% or 94% BCSS at 20 years with 2-5 years versus no tamoxifen, respectively. Guidelines do not yet, however, recommend using this category to abbreviate the length of adjuvant endocrine therapy[33,82].

4C. EndoPredict

EndoPredict® combines a 12-gene RT-PCR assay with tumor size and nodal status to determine the EPclin, a score reflecting the likelihood of distant recurrence at 10 years of ER+, HER2 negative disease with up to 3 positive nodes[96,97]. Patients with a score <3.3 are at low risk for recurrence, and those with a score ≥3.3 are at high risk. Testing can be performed at decentralized labs. The prognostic capability has been validated in both pre-

and postmenopausal women. Indirect comparisons[98] suggest that the EndoPredict genomic assay and EPclin can predict benefit with adjuvant chemotherapy and with neoadjuvant chemo- and endocrine therapy.

In patients disease-free at 5 years and after adjusting for clinical risk factors, EPclin is a significant predictor of recurrence at 5-15 years (HR 2.56; 95% CI 1.88–3.49), regardless of node status (with the caveat that a small number of participants had 15-year follow-up)[99]. EPclin impacts clinical decisions regarding extended endocrine therapy[100] but there is not yet data showing that it can predict the benefit of extended therapy.

4D. ProSigna

ProSigna is a 50-gene signature that assigns an intrinsic subtype and, along with tumor size, node status, and proliferation score, assigns a low, intermediate, or high Risk of Recurrence score[101]. It provides prognostic information for distant recurrence at 10 years for patients with HR+, HER2 negative disease with up to 3 positive nodes. This may impact decisions for chemotherapy or extended endocrine therapy.

Section 5 – Genomic Tumor Evaluation of Hormone Receptor-Positive, HER2 Negative Breast Cancer to Guide Extended Endocrine Therapy

5A. Breast Cancer Index

The Breast Cancer Index (BCI) is a combination of two diagnostic tests—a prognostic Molecular Grade Index and a predictive 2-gene HOX/IL17BR ratio index (H/I), which represents endocrine sensitivity. It estimates late distant recurrence risk for an individual patient, while assessing the potential impact of extended endocrine therapy on that late recurrence risk.

Its predictive value was validated with data from several prospective trials, including the translational-aTTom (Trans-aTTom) study[102], which randomized patients to 5 or 10 years of tamoxifen. Node positive patients who were BCI (H/I)-High had a significantly better recurrence free interval with 10 years of tamoxifen (HR 0.33; 95% CI 0.14–0.75). DFS was also significantly better for those who were BCI (H/I)-High. The BCI similarly predicts the benefit of extended endocrine therapy in node negative patients and with AIs as well[103,104]. It may guide extended therapy decisions in patients with ER+ disease, with 0-3 positive nodes, and who are recurrence-free after 5 years of endocrine therapy.

Section 6– Side Effect Management of Endocrine Therapies

Many of the endocrine therapies have overlapping side effects such as hot flashes, vaginal atrophy, and hair thinning. The management of these symptoms is the same regardless of which drug is responsible for the side effect.

6A. Vasomotor Symptoms

Vasomotor symptoms (VMS) are common in menopausal patients and those on endocrine therapy. The most effective treatment is hormone replacement therapy, which is contraindicated in women on endocrine therapy or with a personal history of breast cancer. The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society (NAMS) summarizes the data on multiple therapies[105].

What does work?

- Gabapentin (dose range 900-2400 mg/day; starting dose 100-300 mg at night)
- Venlafaxine (dose range 37.5-150 mg/day; starting dose 37.5 mg/day)
- Desvenlafaxine (dose range 100-150 mg/day; starting dose 25-50mg/day)
- Paroxetine (dose range 10-25 mg/day; starting dose 10 mg/day) is approved for managing VMS, but may interfere with tamoxifen metabolism through the CYP2D6 metabolic pathway
- Citalopram (dose range 10-20 mg/day; starting dose 10 mg/day)
- Escitalopram (dose range 10-20 mg/day; starting dose 10 mg/day; starting dose 5 mg/day for elderly patients)
- Oxybutynin (dose range 2.5-5 mg twice daily)[106]
- Fezolinetant[107] is a neurokinin 3 (NK3) receptor antagonist recently approved by the FDA to treat moderate to severe hot flashes (dose 45 mg/day)
- Cognitive behavioral therapy[108]
- Weight loss

What does not work?

- Traditional patient counseling has included advice to avoid triggers, such as alcohol, caffeine, spicy foods, hot showers or rooms, and smoking. However, there is no evidence that these behavioral changes reduce VMS[105].
- Similarly, there is no high-quality data showing a benefit with over-the-counter supplements, such as soy-based formulas, black cohosh, wild yam, red clover, and pollen extract[109]. Studies suggesting a benefit are small and safety data is lacking. None are recommended by the North American Menopause Society. There is also concern for drug interactions through the P450 CYP2D6 enzyme system for women taking tamoxifen.
- Studies have not shown a significant benefit with traditional acupuncture, but data is promising for electroacupuncture.

- While exercise is important for overall health, no specific activity has been shown to impact VMS.
- While clonidine may reduce VMS, it is less effective than other prescription therapies and may cause hypotension or, when the drug is stopped, hypertension. The NAMS therefore does not recommend it.

6B. Thromboembolic Events

Tamoxifen is not formally contraindicated for patients with a coagulopathy (such as Protein C or S deficiency or Factor V Leiden) in the absence of a personal history of DVT/PE or anticoagulation requirement. It is important, however, to balance risks and benefits. The risk of VTE may outweigh potential benefit, for instance, in women using tamoxifen for risk reduction; the opposite may be true for women with invasive disease using tamoxifen as protection from disease recurrence (especially those who are not AI candidates). Although not a contraindication, tobacco use further increases the risk of VTE[110].

VTE Risk Reduction

- The half life of tamoxifen is 5-7 days, but the half life of one of its metabolites (N-desmethyltamoxifen) is 14 days[1,111].
- Patients aged 60 years and older, obese patients, and those with a family history of VTE should consider stopping tamoxifen up to 3 weeks before prolonged immobilization (e.g. surgery >90 minutes in duration or with expected postoperative immobilization)[111,112].
- The half life of raloxifene is 27.7-32.5 hours; to reduce the risk of VTE in situations with increased risk, patients should consider stopping raloxifene 72 hours ahead of time[2].

6C. Endometrial hyperplasia, polyps, and cancer

Patients who are receiving or have received tamoxifen and who retain their uterus should undergo annual gynecologic exams. Any change in menstrual bleeding and any postmenopausal vaginal bleeding should prompt a gynecologic evaluation, uterine ultrasound, and possible endometrial biopsy. In the absence of bleeding change or abnormalities, there is no role for routine ultrasound or endometrial biopsies to monitor the endometrium[33].

6D. Vaginal Atrophy/Dyspareunia

Estrogen deprivation results in thin, friable vaginal and vulvar tissue, resulting in tears and fissures, frequent urinary tract infections, dyspareunia, and shortening of the vagina.

Women should avoid potential irritants and regularly use vaginal moisturizers; options include coconut oil and hyaluronic acid products. If these are inadequate, patients can consider vaginal estrogen or dehydroepiandrosterone (DHEA)[113].

While one longitudinal study showed increased breast cancer recurrence risk with vaginal estrogen for women on AIs[114], most data show no impact on cancer recurrence or circulating estrogen levels[115-117]. The preparation and application of vaginal estrogen can impact systemic absorption. Higher systemic absorption is seen with creams (which are applied to a larger area, versus vaginal tablets or rings), application in the upper 2/3 of the vagina (versus the lower third), and with poorer tissue quality (versus estrogenized tissue which results from regular use of vaginal estrogen). The lowest systemic absorption is seen with 10 mcg estradiol tablets and estradiol vaginal rings[113].

Estrogen deprivation-related changes in pelvic anatomy can be addressed with vaginal dilators, biofeedback, and pelvic floor physical therapy[118].

Lubricants are used on an as-needed basis for sexual intercourse and can be water-, silicone-, or oil-based. Patients using condoms for contraception or infection prevention should confirm compatibility between their lubricant and condom material[113].

6E. Osteopenia/Osteoporosis

Tamoxifen can cause bone loss in premenopausal patients[119], but OFS and AIs are the most significant threat to bone density in women on endocrine therapy. Decreased bone density and bone quality leading to fractures is a common complication of AI therapy.

Risk factors for osteoporotic fracture include advanced age, postmenopausal status, low body weight, current tobacco use, heavy alcohol use, history of long-term glucocorticoid use, history of nontraumatic fracture, increased fall risk, immobility, rheumatoid arthritis, and parental hip fracture. Patients with any of these risk factors need bone mineral density (BMD) assessment. Although not validated in cancer patients, tools like FRAX can assess fracture risk in osteopenic patients, identifying those who should receive bone-protective therapy based on clinical fracture risk[120-123].

Patients on AI therapy or OFS should undergo BMD at baseline and at least every 2 years. All patients should be encouraged to consume adequate amounts of calcium and vitamin D, to minimize tobacco and alcohol use, and to engage in balance, flexibility, and weight-bearing exercise as patient status allows.

In general, bone-protective therapy is indicated for patients on AIs/OFS and with:

- Frank osteoporosis (T-score $\leq$2.5 standard deviations or any T-score with a history of fragility fracture),
- Osteopenia and risk factors for fracture (use a higher T-score threshold for patients with multiple risk factors),

- FRAX 10-year major osteoporotic fracture risk of ≥20%,
  or
- FRAX 10-year hip fracture risk ≥3%[33,120,122,123].

Drugs of choice to protect bone health include bisphosphonates (e.g. risedronate, ibandronate, and ZA) and denosumab, a RANK-L inhibitor. Denosumab dosage is 60 mg subcutaneously every 6 months. In the oncology setting (to reduce cancer recurrence), ZA dosage is 4 mg IV every 6 months for 3 years or 4 mg every 3 months for 2 years; osteoporosis dosing is 5 mg IV annually. While bisphosphonates offer cancer-specific benefits (discussed in Section 3F), protect bone density, and may reduce fractures in premenopausal women, more robust data support denosumab for fracture prevention in postmenopausal women[75,120].

ZA may cause a flu-like reaction; both ZA and denosumab can cause osteonecrosis of the jaw. Although this is rare, patients with poor dentition or oral hygiene may be poor candidates for these therapies. ZA has been associated with rare, atypical femur fractures, while cessation of denosumab leads to increased bone turnover and vertebral fracture risk; patients should be transitioned to a bisphosphonate when stopping denosumab to prevent this[75,120,122,123].

As discussed above, bisphosphonates should be offered to all postmenopausal women with invasive breast cancer, independent of bone density, based on a reduced risk of cancer recurrence[75].

6F. Musculoskeletal Complaints

Although SERMs may cause myalgias and arthralgias, arthralgias are common in patients taking an AI. AIs may also contribute to the development of carpal tunnel syndrome or trigger finger. The etiology is unclear but may include inflammatory changes in the joints[124].

Acetaminophen and NSAIDs are useful as-needed treatments. Patients experiencing carpal tunnel syndrome or trigger finger may need wrist splints or joint or tendon injections. Clinical trials have demonstrated the effectiveness of acupuncture and duloxetine for managing AI-related arthralgias[125]. Data suggest that exercise, including yoga, may reduce arthralgias while improving quality of life. Omega 3 fatty acid supplementation may be effective for treating arthralgias, but this benefit may be limited to obese women[126]. Data are mixed regarding vitamin D supplementation. For many patients, a short AI holiday followed by a switch to a different AI will lead to fewer arthralgias.

6G. Weight Gain

Weight gain after breast cancer treatment is common; unfortunately, higher body mass index is associated with poorer breast cancer-specific outcomes[127]. The reasons for weight gain are multifactorial and include receipt of chemotherapy, receipt of endocrine

therapy, postmenopausal status, reduced physical activity, chronic inflammation, and disrupted sleep. Premenopausal women are at higher risk for treatment-associated weight gain than postmenopausal women, as are women who were obese prior to their breast cancer diagnosis, although studies show inconsistent results[128,129].

Similarly, studies evaluating interventions to manage weight in breast cancer patients show inconsistent results. Current data suggest that dietary and/or physical activity interventions are the most successful. Other interventions include cooking classes and counseling[130-132]. The Breast Cancer Weight Loss (BWEL) trial[133] showed that a telephone-based weight loss intervention led to a significant mean 4.8% (±7.9) decrease in body weight at 12 months versus a 0.8% (±6.4) weight gain in controls. Similarly, the InForma trial[132] showed that more participants randomized to a dietary intervention with or without a physical activity intervention lost at least 5% body weight versus participants randomized to a physical activity only intervention or minimal intervention; this weight loss persisted at 12 and 24 months.

Table 1. Randomized clinical trials evaluating endocrine therapy agents for breast cancer risk reduction

Trial profile			Study population	Outcomes		
Trial	**Treatment arms (n)**	**Follow-up (years)**	**Characteristics**	**Primary endpoint**	**BC outcomes RR/HR (95% CI)**	**Other events RR/OR/HR (95% CI)**
NSABP-P1[12,21]	A: Tamoxifen (6681) B: Placebo (6707)	7	Age ≥35 years with 5-year BC risk ≥1.66%* or with LCIS or Age ≥60 years	IBC	IBC RR 0.57 (0.46-0.70)	EndoC RR 3.28 (1.87-6.03); PE RR 2.15 (1.08-4.51); DVT RR 1.44 (0.91-1.34)
IBIS-I[20]	A: Tamoxifen (3579) B: Placebo (3575)	16	Age 35-70 years with increased risk	BC	BC HR 0.71 (0.60-0.83); DCIS HR 0.65 (0.43–1.00)	EndoC OR 3.76 (1.20-15.56)[β]; DVT OR 1.87 (1.11-3.18)[γ]; CVA/CV NS
Royal Marsden[19]	A: Tamoxifen (1250) B: Placebo (1244)	13	Age 30-70 years with a family history	IBC	IBC HR 0.78 (0.58-1.04); ER+ IBC HR 0.48 (0.29-0.79)[α]	EndoC, VTE, stroke NS
Italian[22]	A: Tamoxifen (2700) B: Placebo (2708)	11	Age 35-70 years and s/p hysterectomy	BC	BC RR 0.84 (0.60-1.17); BC RR for high risk women 0.24 (0.10-0.59)	VTE RR 1.63 (1.02-2.62); CVA RR 1.78 (0.70-4.52)
TAM-01[24]	A: Tamoxifen 5 mg (253) B: Placebo (247)	9.7	Age <75 years with ADH, LCIS, or DCIS	BC	BC HR 0.58 (0.35-0.95)	EndoC, VTE NS
MORE[25]	A: Raloxifene 60 mg or 120 mg (5129) B: Placebo (2576)	3.5	Postmenopausal, with osteoporosis, Age ≤80 years	Vertebral fx	IBC RR 0.24 (0.13-0.44)	EndoC RR 0.8 (0.2-2.7); VTE RR 3.1 (1.5-6.2); Vertebral Fx RR 0.7 (0.50-0.80 for 60 mg)
CORE[26]	A: Raloxifene 60 mg (2725) B: Placebo (1286)	8	Extension of MORE	IBC	IBC HR 0.34 (0.22-0.50); NIBC NS	EndoC NS; VTE RR 2.17 (0.83-5.70) during CORE

Trial profile			Study population	Outcomes		
Trial	**Treatment arms (n)**	**Follow-up (years)**	**Characteristics**	**Primary endpoint**	**BC outcomes RR/HR (95% CI)**	**Other events RR/OR/HR (95% CI)**
RUTH[27]	A: Raloxifene (5044) B: Placebo (5057)	5.6	Postmenopausal, Age ≥55 years with CV disease or risk factors for CV disease	IBC and coronary events	IBC HR 0.56 (0.38-0.83)	VTE HR 1.44 (1.06-1.95); Vertebral Fx HR 0.65 (0.47-0.89); CV events NS
STAR[28]	A: Tamoxifen (9872) B: Raloxifene (9975)	9.7	Postmenopausal, Age ≥35 years with 5-year BC risk ≥1.66%* or LCIS	IBC	IBC RR 1.24 (1.05-1.47) for raloxifene; NIBC RR 1.22 (0.95-1.59)	EndoC RR 0.55 (0.36-0.83); VTE RR 0.75 (0.60-0.93)
IBIS-II[29]	A: Anastrozole (1920) B: Placebo (1944)	10.9	Postmenopausal, Age 40-70 years with 10-year risk >5%# or AH, LCIS, or DCIS	BC	BC HR 0.51 (0.39–0.66)	DCIS HR 0.41 (0.22–0.79); Fx OR 1.04 (0.88–1.22)
MAP.3[30]	A: Exemestane (2285) B: Placebo (2275)	3	Postmenopausal, Age ≥60 years or 5-year risk >1.66%* or LCIS, DCIS	IBC	IBC HR 0.35 (0.18- 0.70); BC HR 0.47 (0.27-0.79)	Fx, CV events NS

ADH – atypical ductal hyperplasia; AH – atypical hyperplasia; BC – breast cancer; CI – confidence interval; CV - cardiovascular; DCIS – ductal carcinoma in situ; DVT – deep venous thrombosis; EndoC – endometrial cancer; ER – estrogen receptor; Fx – fracture; HR – hazard ratio; IBC – - invasive breast cancer; LCIS – lobular carcinoma in situ; NA – not available; NIBC – noninvasive breast cancer; NS– not significant; OR – odds ratio; PE – pulmonary embolism; RR – relative risk; Tx – treatment; VTE – venous thromboembolism

* Using the National Cancer Institute Breast Cancer Risk Assessment Tool
# Using the IBIS/Tyrer Cuzick risk model
α Post-treatment period
β Years 0-5
ɣ Years 0-10

Table 2. Randomized clinical trials evaluating ideal length of endocrine therapy

Trial profile			Study population	Outcomes		
Trial	**Treatment arms (n)**	**Follow-up (years)**	**Prior Treatment**	**DFS HR (95% CI)**	**BC outcomes RR/HR (95% CI)**	**Other events RR/HR (95% CI)**
NSABP B-14[48]	A: Tamoxifen (593) x 5 yrs B: Placebo (579)	6.8	Tamoxifen x 5 yrs	NS[#]	OS NS	EndoC RR 2.1 (NS)[#]
ATLAS[50]	A: Tamoxifen (3428) x 5 yrs B: Placebo (3418)	7.6	Tamoxifen x 5 yrs	RR 0.75 (0.62-0.90)[α]	BC mortality RR 0.71 (0.58-0.88)[α]	PE RR 1.87 (1.13-3.07) EndoC RR 1.74 (1.30-2.34)
ATTOM[51]	A: Tamoxifen (3468) x 5 yrs B: Placebo (3485)	NR	Tamoxifen x 5 yrs	RR 0.75 (0.66-0.86)[α]	BC mortality RR 0.77 (0.64-0.92); overall mortality RR 0.86 (0.75-0.97)[α]	EndoC RR 2.20 (1.31-2.34)
MA.17[52]	A: Letrozole x 5 yrs (2583) B: Placebo (2587)*	2.5 yrs	Tamoxifen x 5 yrs	0.58 (0.45-0.76)	Distant DFS HR 0.60 (0.43-0.84); OS HR 0.61 (0.38-0.98) if node positive	No increase in Fx or CV events
NSABP B-33[53]	A: Exemestane x 5 yrs (783) B: Placebo (779)*	2.5	Tamoxifen x 5 yrs	0.68 (4-yr DFS 91% v 89%, P=.07)	RFS HR 0.44 (P=.004); OS NS	No increase in Fx
ABCSG 6a[54]	A: Anastrozole x 3 yrs (387) B: Placebo (469)	5	Tamoxifen x 5 yrs	0.62 (0.40-0.96)	OS NS	-

Trial profile			Study population	Outcomes		
Trial	**Treatment arms (n)**	**Follow-up (years)**	**Prior Treatment**	**DFS HR (95% CI)**	**BC outcomes RR/HR (95% CI)**	**Other events RR/HR (95% CI)**
GIM-4[55]	A:Letrozole x 2-3 yrs (1030) B: Letrozole x 5 yrs (1026)	11.7	Tamoxifen x 2-3 yrs	0.78 (0.65-0.93)	OS HR 0.77 (0.60-0.98)	No increase in Fx
DATA[56]	A: Anastrozole x 3 yrs (955) B: Anastrozole x 6 yrs (957)	10.1	Tamoxifen x 2-3 yrs	0.86 (0.72-1.01)	DFS benefit only if both ER+/PgR+ HR 0.77 (0.63–0.93); OS NS	-
MA.17R[58]	A: Letrozole x 5 yrs B: Placebo	6.3	Tamoxifen x 5 yrs AI x 5 yrs	0.66 (0.48-0.91)	OS NS; Contralateral BC HR 0.42 (0.22-0.81)	Fx 14% v 9% P=.001
IDEAL[59]	A: Letrozole x 2.5 yrs (909) B: Letrozole x 5 yrs (915)	6.6	Tamoxifen/AI x 5 yrs	NS	OS NS	Fewer second BC with longer tx HR 0.39 (0.19-0.81)
ABCSG 16[60]	A: Anastrozole x 2 yrs (1732) B: Anastrozole x 5 yrs (1738)	9.8	Tamoxifen/AI x 5 yrs	NS	OS NS	Fx HR 1.35 (1.00-1.84)
SOLE[61]	A: Continuous letrozole x 5 yrs (2426) B: Intermittent letrozole x 5 yrs (2425)	7	Tamoxifen/AI x 5 yrs	NS	OS NS	-
NSABP B-42[57]	A: Letrozole x 5 yrs (1983)	10.3	Tamoxifen/AI x 5 yrs	HR 0.85 (0.74-0.96)	OS NS	No increase in Fx

Trial profile			Study population	Outcomes		
Trial	**Treatment arms (n)**	**Follow-up (years)**	**Prior Treatment**	**DFS HR (95% CI)**	**BC outcomes RR/HR (95% CI)**	**Other events RR/HR (95% CI)**
	B: Placebo x 5 yrs (1983)					

AI – aromatase inhibitor; BC – breast cancer; CI – confidence interval; DFS – disease-free survival; EndoC – endometrial cancer; ER – estrogen receptor; Fx – fracture; HR – hazard ratio; NS – not significant; NR –- not reported; OS – overall survival; PE – pulmonary embolism; PgR – progesterone receptor; RR – relative risk; Tx – treatment; Yrs – years

* Study unblinded and placebo arm participants offered active therapy
# After 5 years
α After 10 years

NA – not available

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- References -

1. Tamoxifen FDA label. Accessed November 14, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/17970s053lbl.pdf
2. Evista Highlights of Prescribing Information. Accessed November 14, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020815s018lbl.pdf
3. Arimidex. Highlights of prescribing information. Accessed November 14, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020541s026lbl.pdf
4. Femara. Highlights of prescribing information. Accessed November 14. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020726s027lbl.pdf
5. Aromasin. Highlights of prescribing information. Accessed November 14, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020753s020lbl.pdf
6. Faslodex. Highlights of prescribing information. Accessed November 14, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021344s044lbl.pdf
7. Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol.* 2020 Jan 1;6(1):116-124. doi: 10.1001/jamaoncol.2019.4782. PMID: 31563959; PMCID: PMC6777264.
8. Ma CX. ALTernate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment (ALTERNATE) in postmenopausal women: A Phase III Study 2020. Accessed November 14, 2023. https://www.allianceforclinicaltrialsinoncology.org/main/cmsfile?cmsPath=/Public/Annual%20Meeting/files/Alliance%20A011106%20.pdf
9. Orserdu. Highlights of prescribing information. Accessed Noveber 14, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217639s000lbl.pdf
10. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD Trial [published correction appears in *J Clin Oncol.* 2023 Aug 10;41(23):3962]. *J Clin Oncol.* 2022;40(28):3246-3256. doi:10.1200/JCO.22.00338
11. A study evaluating the efficacy and safety of adjuvant giredestrant compared with physician's choice of adjuvant endocrine monotherapy in participants with estrogen receptor-positive, HER2-negative early breast cancer (lidERA Breast Cancer). NCT04961996. Accessed Noveber 14, 2023. https://clinicaltrials.gov/study/NCT04961996
12. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst.* 2005;97(22):1652-1662. doi:10.1093/jnci/dji372
13. Tan-Chiu E, Wang J, Costantino JP, et al. Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. *J Natl Cancer Inst.* 2003;95(4):302-307. doi:10.1093/jnci/95.4.302
14. Eriksson M, Czene K, Conant EF, Hall P. Use of low-dose tamoxifen to increase mammographic screening sensitivity in premenopausal women. *Cancers (Basel).* 2021;13(2):302. Published 2021 Jan 15. doi:10.3390/cancers13020302
15. National Comprehensive Cancer Network Clinical Guidelines in Oncology. Breast Cancer risk Reduction version 1.2024. Accessed

November 14, 2023. https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf
16. Visvanathan K, Fabian CJ, Bantug E, et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol.* 2019;37(33):3152-3165. doi:10.1200/JCO.19.01472
17. Smith SG, Sestak I, Forster A, et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. *Ann Oncol.* 2016;27(4):575-590. doi:10.1093/annonc/mdv590
18. Freedman AN, Yu B, Gail MH, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older [published correction appears in *J Clin Oncol.* 2013 Nov 10;31(32):4167]. *J Clin Oncol.* 2011;29(17):2327-2333. doi:10.1200/JCO.2010.33.0258
19. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst.* 2007;99(4):283-290. doi:10.1093/jnci/djk050
20. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol.* 2015;16(1):67-75. doi:10.1016/S1470-2045(14)71171-4
21. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* Sep 16 1998;90(18):1371-88. doi:10.1093/jnci/90.18.1371
22. Veronesi U, Maisonneuve P, Rotmensz N, et al. Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. *J Natl Cancer Inst.* 2003;95(2):160-165. doi:10.1093/jnci/95.2.160
23. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet.* 2003;361(9354):296-300. doi:10.1016/S0140-6736(03)12342-2
24. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent recurrence in breast noninvasive neoplasia: a 10-year follow-up of TAM-01 Study. *J Clin Oncol.* 2023;41(17):3116-3121. doi:10.1200/JCO.22.02900
25. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation [published correction appears in *JAMA.* 1999 Dec 8;282(22):2124]. *JAMA.* 1999;281(23):2189-2197. doi:10.1001/jama.281.23.2189
26. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst.* 2004;96(23):1751-1761. doi:10.1093/jnci/djh319
27. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med.* 2006;355(2):125-137. doi:10.1056/NEJMoa062462
28. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. *Cancer Prev Res (Phila).* 2010;3(6):696-706. doi:10.1158/1940-6207.CAPR-10-0076
29. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial [published correction appears in *Lancet.* 2020 Feb 15;395(10223):496] [published correction appears in *Lancet.* 2021 Feb 27;397(10276):796]. *Lancet.* 2020;395(10218):117-122. doi:10.1016/S0140-6736(19)32955-1
30. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women [published correction appears in *N Engl J Med.* 2011 Oct 6;365(14):1361]. *N Engl J Med.* 2011;364(25):2381-2391. doi:10.1056/NEJMoa1103507
31. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol.* 2010;11(12):1135-1141. doi:10.1016/S1470-2045(10)70257-6
32. Goss PE. Letrozole in the extended adjuvant setting: MA.17 [published correction appears in *Breast Cancer Res Treat.* 2008 Nov;112(2):369]. *Breast Cancer Res Treat.* 2007;105 Suppl 1(Suppl 1):45-53. doi:10.1007/s10549-007-9698-1
33. National Comprehensive Cancer Network Clinical Guidelines in Oncology. Breast Cancer version 4.2023. Accessed November 14, 2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
34. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353(9169):1993-2000. doi:10.1016/S0140-6736(99)05036-9
35. Margolese RG, Cecchini RS, Julian TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet.* 2016;387(10021):849-856. doi:10.1016/S0140-6736(15)01168-X
36. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised

ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet.* 2016;387(10021):866-873. doi:10.1016/S0140-6736(15)01129-0

37. Francis PA, Fleming GF, Láng I, et al. Adjuvant endocrine therapy in premenopausal breast cancer: 12-year results from SOFT [published correction appears in *J Clin Oncol.* 2023 Sep 1;41(25):4187]. *J Clin Oncol.* 2023;41(7):1370-1375. doi:10.1200/JCO.22.01065
38. Pagani O, Walley BA, Fleming GF, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer: long-term follow-up of the combined TEXT and SOFT Trials. *J Clin Oncol.* 2023;41(7):1376-1382. doi:10.1200/JCO.22.01064
39. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO Guideline. *J Clin Oncol.* 2021;39(13):1485-1505. doi:10.1200/JCO.20.03399
40. Masuda N, Sagara Y, Kinoshita T, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. *Lancet Oncology.* 2012/04/01/ 2012;13(4):345-352. doi: 10.1016/S1470-2045(11)70373-4
41. Semiglazov V, Kletsel A, Semiglazov V, et al. Exemestane (E) vs tamoxifen (T) as neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer (T2N1–2, T3N0–1, T4N0M0). *J Clin Oncol.* 2005;23(16_suppl):530-530. doi:10.1200/jco.2005.23.16_suppl.530 (20 RUSSIAN)
42. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial [published correction appears in Breast Cancer Res Treat. 2008 Nov;112(2):371]. *Breast Cancer Res Treat.* 2007;105 Suppl 1(Suppl 1):33-43. doi:10.1007/s10549-007-9701-x
43. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. *JAMA Oncol.* 2016;2(11):1477-1486. doi:10.1001/jamaoncol.2016.1897
44. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial [published correction appears in *Lancet Oncol.* 2020 Dec;21(12):e553]. *Lancet Oncol.* 2020;21(11):1443-1454. doi:10.1016/S1470-2045(20)30458-7
45. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst.* 2008;100(19):1380-1388. doi:10.1093/jnci/djn309
46. Nitz UA, Gluz O, Kümmel S, et al. Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2- early breast cancer. *J Clin Oncol.* 2022;40(23):2557-2567. doi:10.1200/JCO.21.02759
47. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 1998;351(9114):1451-1467.
48. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst.* 2001;93(9):684-690. doi:10.1093/jnci/93.9.684
49. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol.* 2019;37(5):423-438. doi:10.1200/JCO.18.01160
50. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial [published correction appears in *Lancet.* 2013 Mar 9;381(9869):804] [published correction appears in Lancet. 2017 May 13;389(10082):1884]. *Lancet.* 2013;381(9869):805-816. doi:10.1016/S0140-6736(12)61963-1
51. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol. 2013;31(18)suppl (June 20, 2013) 5-5. Published online June 20, 2013.
52. Goss PE. Letrozole in the extended adjuvant setting: MA.17 [published correction appears in *Breast Cancer Res Treat.* 2008 Nov;112(2):369]. *Breast Cancer Res Treat.* 2007;105 Suppl 1(Suppl 1):45-53. doi:10.1007/s10549-007-9698-1
53. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol.* 2008;26(12):1965-1971. doi:10.1200/JCO.2007.14.0228
54. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a [published correction appears in *J Natl Cancer Inst.* 2008 Feb 6;100(3):226]. *J Natl Cancer Inst.* 2007;99(24):1845-1853. doi:10.1093/jnci/djm246

55. Del Mastro L, Mansutti M, Bisagni G, et al. Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021;22(10):1458-1467. doi:10.1016/S1470-2045(21)00352-1
56. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial [published correction appears in *Lancet Oncol.* 2017 Nov;18(11):e642]. *Lancet Oncol.* 2017;18(11):1502-1511. doi:10.1016/S1470-2045(17)30600-9
57. Mamounas EP, Bandos H, Rastogi P, et al. Ten-year update: NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-42 randomized trial: extended letrozole therapy in early-stage breast cancer [published correction appears in *J Natl Cancer Inst.* 2023 Sep 27;:]. *J Natl Cancer Inst.* 2023;115(11):1302-1309. doi:10.1093/jnci/djad078
58. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med.* 2016;375(3):209-219. doi:10.1056/NEJMoa1604700
59. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL Trial (BOOG 2006-05). *J Natl Cancer Inst.* 2018;110(1):10.1093/jnci/djx134. doi:10.1093/jnci/djx134
60. Gnant M, Fitzal F, Rinnerthaler G, et al. Duration of adjuvant aromatase-inhibitor therapy in postmenopausal breast cancer. *N Engl J Med.* 2021;385(5):395-405. doi:10.1056/NEJMoa2104162
61. Jerusalem G, Farah S, Courtois A, et al. Continuous versus intermittent extended adjuvant letrozole for breast cancer: final results of randomized phase III SOLE (Study of Letrozole Extension) and SOLE Estrogen Substudy. *Ann Oncol.* 2021;32(10):1256-1266. doi:10.1016/j.annonc.2021.07.017
62. Partridge AH, Niman SM, Ruggeri M, et al; International Breast Cancer Study Group; POSITIVE trial collaborators. interrupting endocrine therapy to attempt pregnancy after breast cancer. *N Engl J Med.* 2023 May 4;388(18):1645-1656. doi: 10.1056/NEJMoa2212856. PMID: 37133584; PMCID: PMC10358451.
63. Diab S. G., Elledge R. M., Clark G. M. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst.* 2000;92(7):550–556. doi: 10.1093/jnci/92.7.550.
64. Bertolo A, Rosso C, Voutsadakis IA. Breast cancer in patients 80 years-old and older. *Eur J Breast Health.* 2020;16(3):208-212. Published 2020 May 21. doi:10.5152/ejbh.2020.5659
65. Chakrabarti J, Kenny FS, Syed BM, Robertson JF, Blamey RW, Cheung KL. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up. *Crit Rev Oncol Hematol.* 2011;78(3):260-264. doi:10.1016/j.critrevonc.2010.04.006
66. Morgan J, Wyld L, Collins KA, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). *Cochrane Database Syst Rev.* 2014;5(5):CD004272. Published 2014 May 19. doi:10.1002/14651858.CD004272.pub3
67. Gazet JC, Sutcliffe R. A randomised trial comparing tamoxifen vs. surgery in patients over the age of 70 with operable breast cancer--final results after 28 years of follow-up. *Eur J Surg Oncol.* 2011;37(9):754-757. doi:10.1016/j.ejso.2011.06.011
68. Johnston SJ, Kenny FS, Syed BM, et al. A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up. *Ann Oncol.* 2012;23(9):2296-2300. doi:10.1093/annonc/mdr630
69. Syed BM, Al-Khyatt W, Johnston SJ, et al. Long-term clinical outcome of oestrogen receptor-positive operable primary breast cancer in older women: a large series from a single centre. *Br J Cancer.* 2011 Apr 26;104(9):1393-400. doi: 10.1038/bjc.2011.105. Epub 2011 Mar 29. PMID: 21448163; PMCID: PMC3101924.
70. Cancer and Aging Research Group Chemotherapy Toxicity Tool (www.mycarg.org). Accessed November 16, 2023. https://www.mycarg.org/?page_id=2405
71. University of California San Francisco ePrognosis. Accessed November 16, 2023. https://eprognosis.ucsf.edu/about.php
72. American College of Surgeons' NSQIP Surgical Risk Calculator version 4.0. Accessed November 16, 2023. https://riskcalculator.facs.org/RiskCalculator/
73. Hassett MJ, Somerfield MR, Baker ER, et al. Management of male breast cancer: ASCO guideline. *J Clin Oncol.* 2020 Jun 1;38(16):1849-1863. doi: 10.1200/JCO.19.03120. Epub 2020 Feb 14. PMID: 32058842.
74. Liu Y, Zhao S, Zhang Y, Onwuka JU, Zhang Q, Liu X. Bisphosphonates and breast cancer survival: a meta-analysis and trial sequential analysis of 81508 participants from 23 prospective epidemiological studies. *Aging* (Albany NY). 2021:13(15):19835-19866. doi: 10.18632/aging.203395. Epub 2021 Aug 10. PMID: 34375305; PMCID: PMC8386537.
75. Eisen A, Somerfield MR, Accordino MK, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH

(CCO) guideline update. *J Clin Oncol*. 2022;40(7):787-800. doi:10.1200/JCO.21.02647
76. Predict. Accessed November 16, 2023. https://breast.predict.nhs.uk/tool
77. Friedl TWP, Fehm T, Müller V, et al. Prognosis of patients with early breast cancer receiving 5 years vs 2 years of adjuvant bisphosphonate treatment: a phase 3 randomized clinical trial. *JAMA Oncol*. 2021;7(8):1149-1157. doi:10.1001/jamaoncol.2021.1854
78. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90. doi:10.1016/S1470-2045(22)00694-5
79. Kisqali Highlights of Prescribing Information. Accessed November 16, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209092s013,209935s021lbl.pdf
80. Ibrance Highlights of Prescribing Information. Accessed November 16, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207103s008lbl.pdf
81. Jakubowski DM, Bailey H, Abran J, et al. Molecular characterization of breast cancer needle core biopsy specimens by the 21-gene Breast Recurrence Score test. *J Surg Oncol*. 2020 Jun 4;122(4):611–8. doi: 10.1002/jso.26050. Epub ahead of print. PMID: 32497318; PMCID: PMC7496790.
82. Andre F, Ismaila N, Allison KH, et al. Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO guideline update [published correction appears in *J Clin Oncol*. 2022 Aug 1;40(22):2514]. *J Clin Oncol*. 2022;40(16):1816-1837. doi:10.1200/JCO.22.00069
83. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351(27):2817-2826. doi:10.1056/NEJMoa041588
84. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121. doi:10.1056/NEJMoa1804710
85. Sparano J, Gray RJ, Makower D, et al. Trial assigning individualized options for treatment (TAILORx): an update including 12-year event rates [abstract]. In: Proceedings of the 2022 San Antonio Breast Cancer Symposium; 2022 Dec 6-10; San Antonio, TX. Philadelphia (PA): *AACR; Cancer Res*. 2023;83(5 Suppl):Abstract nr GS1-05.
86. Albain KS, Gray RJ, Makower DF, et al. Race, ethnicity, and clinical outcomes in hormone receptor-positive, HER2-negative, node-negative breast cancer in the randomized TAILORx trial. *J Natl Cancer Inst*. 2021;113(4):390-399. doi:10.1093/jnci/djaa148
87. Hoskins KF, Danciu OC, Ko NY, Calip GS. Association of race/ethnicity and the 21-gene recurrence score with breast cancer-specific mortality among US women. *JAMA Oncol*. 2021;7(3):370-378. doi:10.1001/jamaoncol.2020.732
88. Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385(25):2336-2347. doi:10.1056/NEJMoa2108873
89. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol*. 2010;11(1):55-65. doi:10.1016/S1470-2045(09)70314-6
90. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*. 2002;347(25):1999-2009. doi:10.1056/NEJMoa021967
91. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729. doi:10.1056/NEJMoa1602253
92. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol*. 2021;22(4):476-488. doi:10.1016/S1470-2045(21)00007-3
93. Lopes Cardozo JMN, Drukker CA, Rutgers EJT, et al. Outcome of patients with an ultralow-risk 70-gene signature in the MINDACT trial. *J Clin Oncol*. 2022;40(12):1335-1345. doi:10.1200/JCO.21.02019
94. Delahaye LJMJ, Drukker CA, Dreezen C, et al. A breast cancer gene signature for indolent disease. *Breast Cancer Res Treat*. 2017;164(2):461-466. doi:10.1007/s10549-017-4262-0
95. Esserman LJ, Yau C, Thompson CK, et al. Use of molecular tools to identify patients with indolent breast cancers with ultralow risk over 2 decades [published correction appears in *JAMA Oncol*. 2017 Nov 1;3(11):1589]. *JAMA Oncol*. 2017;3(11):1503-1510. doi:10.1001/jamaoncol.2017.1261
96. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res*. 2011;17(18):6012-6020. doi:10.1158/1078-0432.CCR-11-0926
97. Constantinidou A, Marcou Y, Toss MS, et al. Clinical validation of EndoPredict in pre-menopausal women with er-positive, HER2-negative primary breast cancer. *Clin Cancer Res*. 2022;28(20):4435-4443. doi:10.1158/1078-0432.CCR-22-0619

98. Sestak I, Martín M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* 2019;176(2):377-386. doi:10.1007/s10549-019-05226-8
99. Filipits M, Dubsky P, Rudas M, et al. Prediction of distant recurrence using EndoPredict among women with ER+, HER2- node-positive and node-negative breast cancer treated with endocrine therapy only. *Clin Cancer Res.* 2019;25(13):3865-3872. doi: 10.1158/1078-0432.CCR-19-0376.
100. Brufsky A, Lenz L, Pudusseri A, et al. Adherence to EndoPredict test scores for extended endocrine therapy management in the prospective EndoPredict Extended Endocrine Trial (EXET). *J Clin Oncol.*2022;40, (suppl 16; abstr 537) DOI:10.1200/JCO.2022.40.16_suppl.537
101. Gnant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Ann Oncol.* 2014;25(2):339-345. doi:10.1093/annonc/mdt494
102. Bartlett JMS, Sgroi DC, Treuner K, et al. Breast Cancer Index is a predictive biomarker of treatment benefit and outcome from extended tamoxifen therapy: final analysis of the Trans-aTTom Study. *Clin Cancer Res.* 2022;28(9):1871-1880. doi:10.1158/1078-0432.CCR-21-3385
103. Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. *J Natl Cancer Inst.* 2013;105(14):1036-1042. doi:10.1093/jnci/djt146
104. Noordhoek I, Treuner K, Putter H, et al. Breast Cancer Index predicts extended endocrine benefit to individualize selection of patients with hr+ early-stage breast cancer for 10 years of endocrine therapy. *Clin Cancer Res.* 2021;27(1):311-319. doi:10.1158/1078-0432.CCR-20-2737
105. The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause.* 2023;30(6):573-590. doi:10.1097/GME.0000000000002200
106. Leon-Ferre RA, Novotny PJ, Wolfe EG, et al. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). *JNCI Cancer Spectr.* 2019;4(1):pkz088. Published 2019 Oct 21. doi:10.1093/jncics/pkz088
107. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet.* 2023;401(10382):1091-1102. doi:10.1016/S0140-6736(23)00085-5
108. Hunter MS. Cognitive behavioral therapy for menopausal symptoms. *Climacteric.* 2021;24(1):51-56. doi:10.1080/13697137.2020.1777965
109. Johnson A, Roberts L, Elkins G. Complementary and alternative medicine for menopause. *J Evid Based Integr Med.* 2019;24:2515690X19829380. doi:10.1177/2515690X19829380
110. Decensi A, Maisonneuve P, Rotmensz N, et al. Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. *Circulation.* 2005;111(5):650-656. doi:10.1161/01.CIR.0000154545.84124.AC
111. Farrar MC, Jacobs TF. Tamoxifen. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532905/
112. Hussain T, Kneeshaw PJ. Stopping tamoxifen peri-operatively for VTE risk reduction: a proposed management algorithm. *Int J Surg.* 2012;10(6):313-316. doi:10.1016/j.ijsu.2012.05.001
113. Sussman TA, Kruse ML, Thacker HL, Abraham J. Managing genitourinary syndrome of menopause in breast cancer survivors receiving endocrine therapy. *J Oncol Pract.* 2019;15(7):363-370. doi:10.1200/JOP.18.00710
114. Cold S, Cold F, Jensen MB, Cronin-Fenton D, Christiansen P, Ejlertsen B. Systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study. *J Natl Cancer Inst.* 2022;114(10):1347-1354. doi:10.1093/jnci/djac112
115. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol.* 201;3(3):313-319. doi: 10.1001/jamaoncol.2016.3904. Erratum in: *JAMA Oncol.* 2020;6(9):1473. PMID: 27832260.
116. Sánchez-Rovira P, Hirschberg AL, Gil-Gil M, Bermejo-De Las Heras B, Nieto-Magro C. A phase ii prospective, randomized, double-blind, placebo-controlled and multicenter clinical trial to assess the safety of 0.005% estriol vaginal gel in hormone receptor-positive postmenopausal women with early stage breast cancer in treatment with aromatase inhibitor in the adjuvant setting. *Oncologist.* 2020 Dec;25(12):e1846-1854. Doi: 10.1634/theoncologist.2020-0417. Epub 2020 Jun 9. PMID: 32459035; PMCID: PMC8108054.
117. Pavlović RT, Janković SM, Milovanović JR, et al. The safety of local hormonal treatment for vulvovaginal atrophy in women with estrogen receptor-positive breast cancer who are on adjuvant aromatase inhibitor therapy: meta-

analysis. *Clin Breast Cancer*. 2019 Dec;19(6):e731-e740. doi: 10.1016/j.clbc.2019.07.007. Epub 2019 Aug 21. PMID: 31522958.

118. Kagan R, Kellogg-Spadt S, Parish SJ. Practical treatment considerations in the management of genitourinary syndrome of menopause. *Drugs Aging*. 2019;36(10):897-908. doi:10.1007/s40266-019-00700-w
119. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol*. 1996;14(1):78-84. doi:10.1200/JCO.1996.14.1.78
120. Shapiro CL, Van Poznak C, Lacchetti C, et al. Management of osteoporosis in survivors of adult cancers with nonmetastatic disease: ASCO clinical practice guideline. *J Clin Oncol*. 2019;37(31):2916-2946. doi:10.1200/JCO.19.01696
121. FRAX Fracture Risk Assessmenet Tool. Accessed November 16, 2023. https://frax.shef.ac.uk/FRAX/index.aspx
122. Waqas K, Lima Ferreira J, Tsourdi E, Body JJ, Hadji P, Zillikens MC. Updated guidance on the management of cancer treatment-induced bone loss (CTIBL) in pre- and postmenopausal women with early-stage breast cancer. *J Bone Oncol*. 2021;28:100355. Published 2021 Mar 18. doi:10.1016/j.jbo.2021.100355
123. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2020;31(12):1650-1663. doi:10.1016/j.annonc.2020.07.019
124. Gupta A, Henry NL, Loprinzi CL. Management of aromatase inhibitor-induced musculoskeletal symptoms. *JCO Oncol Pract*. 2020;16(11):733-739. doi:10.1200/OP.20.00113
125. Bae K, Lamoury G, Carroll S, et al. Comparison of the clinical effectiveness of treatments for aromatase inhibitor-induced arthralgia in breast cancer patients: A systematic review with network meta-analysis. *Crit Rev Oncol Hematol*. 2023;181:103898. doi:10.1016/j.critrevonc.2022.103898
126. Shen S, Unger JM, Crew KD, et al. Omega-3 fatty acid use for obese breast cancer patients with aromatase inhibitor-related arthralgia (SWOG S0927). *Breast Cancer Res Treat*. 2018;172(3):603-610. doi:10.1007/s10549-018-4946-0
127. Nichols HB, Trentham-Dietz A, Egan KM, et al. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev*. 2009;18(5):1403-1409. doi:10.1158/1055-9965.EPI-08-1094
128. Uhelski AR, Blackford AL, Sheng JY, et al. Factors associated with weight gain in pre- and post-menopausal women receiving adjuvant endocrine therapy for breast cancer [published online ahead of print, 2023 Jun 1]. *J Cancer Surviv*. 2023;10.1007/s11764-023-01408-y. doi:10.1007/s11764-023-01408-y
129. Nyrop KA, Williams GR, Muss HB, Shachar SS. Weight gain during adjuvant endocrine treatment for early-stage breast cancer: What is the evidence?. *Breast Cancer Res Treat*. 2016;158(2):203-217. doi:10.1007/s10549-016-3874-0
130. Thomson ZO, Reeves MM. Can weight gain be prevented in women receiving treatment for breast cancer? A systematic review of intervention studies. *Obes Rev*. 2017;18(11):1364-1373. doi:10.1111/obr.12591
131. Reeves MM, Terranova CO, Eakin EG, Demark-Wahnefried W. Weight loss intervention trials in women with breast cancer: a systematic review. *Obes Rev*. 2014;15(9):749-768. doi:10.1111/obr.12190
132. Gnagnarella P, Dragà D, Raja S, et al. Physical activity and/or dietary intervention in overweight or obese breast cancer survivors: results of the InForma randomized trial [published online ahead of print, 2023 Jul 7]. *J Cancer Surviv*. 2023;10.1007/s11764-023-01415-z. doi:10.1007/s11764-023-01415-z
133. Delahanty LM, Wadden TA, Goodwin PJ, et al. The Breast Cancer Weight Loss trial (Alliance A011401): A description and evidence for the lifestyle intervention. *Obesity (Silver Spring)*. 2022;30(1):28-38. doi:10.1002/oby.23287

